REMARKS

The applicants acknowledge the Non-Final Office Action, dated November 5, 2007, with appreciation. The Office indicates that Claims 11-18 are pending in the application and are presently under examination. The Applicants acknowledge the Office withdrawal of the rejections of the May 3, 2007 Office Action. Moreover, the Applicants' representatives acknowledge the gracious interview provided by both Examiner FORD and Supervisory Patent Examiner FOLEY on January 3, 2008.

OBVIOUSNESS UNDER 35 USC § 103:

The Office rejects Claims 11 and 14-15 under 35 U.S.C. § 103(a) as being obvious over the disclosure of Keen, et al. (Plastic and Reconstructive Surgery,1994, 94:94-99) in view of Johnson, et al. (U.S. Patent No. 5,512,547). The Office indicates that Keen, et al. teach a method of treating patents who have hyperkinetic facial lines with botulinum toxin A. The Office further notes that Keen, et al. do not teach the instant claim limitations to "a botulinum neurotoxin which is free of the complexing proteins" and "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes".

In an effort to cure this deficit of disclosure, the Office rejection combines the Keen, et al. disclosure with that of Johnson, et al., who teach a pharmaceutical composition comprising an essentially pure botulinum toxin A. The Office characterizes Johnson, et al. as teaching the use of pure neurotoxin instead of the toxin complex to reduce the amount of toxin required to obtain the number of necessary active units per vial, and that this improvement also reduces the amount of inactive toxin in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients. The Office concludes that "It would be expected absent, evidence to the contrary, that a composition comprising pure botulinum toxin A (without complexing proteins) would be effective in treating patients that are nonresponders (have neutralizing antibodies to botulinum toxin A complex)".

Significantly and critically, Keen, et al. and Johnson, et al. do not teach or suggest the instant claim limitation to administration of a *Clostridium botulinum* neurotoxin which is free of complexing proteins in subjects already exhibiting neutralizing antibodies. In fact, the Keen, et al. and Johnson, et al. disclosures teach that subjects who have developed neutralizing antibodies would not benefit from treatment with botulinum neurotoxins. At Column 2, lines 51-55, Johnson, et al. state that, "The toxin is recognized by patient's immune systems as foreign and stimulates antibody production. This renders treatment of the various hyperactive muscle disorders with botulinum toxin ineffective." Consequently, Johnson, et al. teach away from administering a *Clostridium botulinum* neurotoxin free from complexing proteins to patients who have developed neutralizing antibodies.

The Johnson, et al. disclosure actually pertains to the development of a shelf-stable botulinum neurotoxin composition for preventing the development of neutralizing antibodies. Johnson, et al. state that, "This improvement also reduces the amount of inactive toxin (toxoid) in each vial and thereby lessens the possibility of antibody formation after injection of the preparation into patients." at Column 2, lines 47-51. Moreover, Johnson, et al. administer various *Clostridium botulinum* neurotoxin formulations to naïve animals to assess the development of antibodies and conclude that no neutralizing antibodies are formed in the subject animals when shelf-stable formulations of the invention are administered (Table 3). Johnson, et al. do not disclose or teach administration of a botulinum neurotoxin which is free from complexing proteins to animals which already exhibit neutralizing antibodies. Thus, the Office position that, "It would be expected absent, evidence to the contrary, that a composition comprising pure botulinum toxin A (without complexing proteins) would be effective in treating patients that are nonresponders (have neutralizing antibodies to botulinum toxin A complex)" finds no basis in the prior art disclosure of record.

The Office goes on to reject Claims 11-15 under 35 U.S.C. § 103(a) as being obvious over the disclosure of Carruthers, et al. (Cosmetic Uses of Botulinum Toxin A Exotoxin, In: Klein AW, ed. *Tissue Augmentation in Clinical Practice: Procedures and*

Techniques. New York: Marcel Dekker, 1998, p. 207-236) in view of Heckman, et al. (Arch. Dermatol., 1998, 134:1298-1299) and further in view of Johnson, et al. (U.S. Patent No. 5,512,547). The Office basis for the rejection over Johnson, et al. is stated above, with Carruthers, et al. being cited for teaching a method of treating a cosmetic condition treatable with a botulinum toxin, specifically, wrinkling. The Office cites Heckman, et al. for teaching botulinum toxin complex treatment for hyperhidrosis. The Office nonetheless admits that Carruthers, et al. and Heckman, et al. do not teach the instant claim limitations to "a botulinum neurotoxin which is free of the complexing proteins" and "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes".

The Office rejects Claims 16-18 under 35 U.S.C. § 103(a) as being obvious over the disclosure of Kessler, et al. (J. Neurol., 1999, 246:265-274) in view of Johnson, et al. (U.S. Patent No. 5,512,547). The Office basis for the rejection over Johnson, et al. is stated above, with Kessler, et al. being cited for teaching a long-term treatment of cervical dystonia with botulinum toxin A complex and the development of antibodies against the toxin. The Office nonetheless admits that Kessler, et al. do not teach the instant claim limitations to "a botulinum neurotoxin which is free of the complexing proteins" and "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes".

The Office rejects Claims 16-18 under 35 U.S.C. § 103 for obviousness over Göschel, et al., (Experimental Neurology 1997, 147:96-102) in view of Johnson, et al. (U.S. Patent No. 5,512,547). The Office basis for the rejection over Johnson, et al. is stated above. Göschel, et al. is cited for teaching botulinum toxin therapy for the various dystonias and disorders which are recited in the claims. The Office admits that Göschel, et al. teach that patients develop neutralizing antibodies against botulinum toxin A complex and that neutralizing antibodies are the cause of therapeutic failure. The Office nonetheless admits that Göschel, et al. do not teach the instant claim limitations to "a botulinum neurotoxin which is free of the complexing proteins" and "wherein the human or animal already exhibits neutralizing antibodies against botulinum neurotoxin complexes".

The Applicants submit that the Office has not identified a prior art reference or combination of references which fulfill the basic requirements for establishing *prima facie* obviousness. The primary reference applied in combination with other prior art references, Johnson, et al., is cited for teaching preparations of a purified botulinum neurotoxin which is free from complexing proteins. Johnson, et al. teach the use of these preparations to reduce the possibility of antibody formation after injection into naïve patients. This teaching does not, however, extend to the surprising discovery that a botulinum neurotoxin preparation free from complexing proteins will be effective in treating subjects already exhibiting neutralizing antibodies, which is the subject of the instant invention.

The Applicants submit that the Office is relying on improper hindsight reasoning. The fact that "Johnson, et al. teach that purified botulinum neurotoxin preparations (free from complexing proteins) lessens the possibility of antibody formation after injection of the preparation into patients" is laudable, but not relevant to the instant inquiry. The Office must establish that one skilled in the art actually has taught, or may infer from the combined disclosure of record, administration of a *Clostridium botulinum* neurotoxin which is free from complexing proteins for the treatment of subjects already exhibiting neutralizing antibodies against botulinum neurotoxin complexes, which is the instant invention. In fact, the art of record acknowledge the futility of therapy in such patients and seek to develop therapies which avoid the possibility of neutralizing antibody formation and the resulting therapeutic failure.

In light of these remarks, the Applicants submit the Office has not established a *prima facie* basis for obviousness. Reconsideration of each ground of rejection and withdrawal of the rejection is respectfully requested.

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Accordingly, entry of the Response, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

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